RECENT ADVANCES IN CHILDHOOD DIABETES MELLITUS
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SUMMARY
Diabetes mellitus (DM) is a syndrome characterized by disturbed metabolism of carbohydrate, protein, and fat. It is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin. It presents with very different medical and psychosocial issues in children.

Epidemiological studies indicate that there is gradual but steady increase in the incidence of both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) in both developed and developing countries. The manifestations, therapy goals, clinical course, susceptibility to complications of diabetes differ among childhood cases.

T1DM accounts for the majority of cases of diabetes in children. Diabetic ketoacidosis may be the initial presentation of T1DM in many children particularly in Africa probably due to low level of awareness.

The focus of this review on T1DM is to provide an overview of the major advances in the aetiology, pathogenesis, and clinical management of newly diagnosed children and their subsequent management with the aim of ensuring optimal growth and development as well as preventing acute and chronic complications. The advances in insulin therapy and regimens and the presentation and management of diabetic ketoacidosis are discussed. The prospects for the cure of the disease are also highlighted in this review.

INTRODUCTION
Diabetes is a Greek word which means 'to pass through 'urine'. It is a syndrome characterized by disturbed metabolism of carbohydrate, protein, and fat as a result of absolute insulin deficiency (Type 1 diabetes mellitus) or relative insulin deficiency and resistance (Type 2 diabetes). It is the most common endocrine/metabolic disorder of childhood and adolescence. Diabetes can occur in all ages in children.

Classification of Diabetes
DM is a heterogeneous entity which was first classified by the American Diabetes Association in 1979 on the basis of aetiopathogenesis into four groups, mainly Type1, Type 2, Other types and Gestational diabetes. Table 1 is classification modified from 'Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus' in 2000 reflecting all major categories in childhood, including the emergence of type 2 diabetes mellitus (T2DM) and other causes of type 1 diabetes mellitus (T1DM).[1-2]

Type 1 Diabetes Mellitus (T1DM) refers to childhood diabetes usually associated with autoimmunity and absolute insulin deficiency, although insulin deficiency may not be absolute at clinical onset of the disease.[3] T1DM is further subclassified into Type 1A associated with the presence of islet cell autoantibodies, and Type 1B characterized by the absence of the antibodies.[2-3] Type 2 Diabetes Mellitus (T2DM) is childhood diabetes associated with obesity and insulin resistance. Maturity-onset diabetes of youth (MODY), an autosomal dorminant DM, is a "milder" form of diabetes caused by specific gene defects that impair insulin secretion.[4] The more severe forms of MODY may require insulin subsequently. Neonatal diabetes is uncommon and usually transient. Permanent neonatal DM has been described, which is usually familial and nonautoimmune.[5]

This review, which focuses mainly on T1DM, provides an overview of the major advances in the understanding of the aetiology, pathogenesis and clinical management of DM in children.

I. Type 1 diabetes (beta cell destruction ultimately leading to complete insulin deficiency)
- A. Immune mediated
- B. Idiopathic

II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
- A. Typical
- B. Atypical

III. Genetic defects of ß cell function
- A. MODY syndromes
  1. MODY 1 Chromosome 20, HNF-4á
  2. MODY 2 Chromosome 7, glucokinase
  3. MODY 3 Chromosome 12, HNF - 1 á
  4. MODY 4 Chromosome 13, IPF – 1
  5. MODY 5 Chromosome 17, HNF - 1ß, TCF – 2
  6. MODY 6 Chromosome 2q32, Neuro-D1/Beta-2
- B. Mitochondrial DNA mutations (includes one form of Wolfram syndrome; Pearson syndrome; Kearns-Sayre, diabetes mellitus deafness)
- C. Wolfram syndrome – DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness): WFSI-Wolfram- chromosome.
  1. Wolfram locus 2- chromosome
  2. Wolfram mitochondrial
- D. Thiamine responsive

IV. Drug or chemical induced
- A. Antirejection – cyclosporine
- B. Glucocorticoids (with impaired insulin secretion, e.g., cystic fibrosis)
- C. L- Asparaginase
- D. ß – Adrenergic blockers
- E. Vacor (rodenticide)
- F. Phenytoin (Dilantin)
- G. Alfa-Interferon
- H. Diazoxide
- I. Nicotinic acid
- J. Others

V. Diseases of exocrine pancreas
- A. Cystic fibrosis-related diabetes
- B. Trauma-pancreatectomy
- C. Pancreatitis-ionizing radiation
- D. Others

VI. Infections
- A. Congenital rubella
- B. Cytomegalovirus
- C. Hemolytic-uremic syndrome

VII. Variants of type 2 diabetes
- A. Genetic defects of insulin action
  1. Rabson-Mendenhall syndrome
  2. Leprechaunism
  3. Lipoatrophic diabetes syndrome
  4. Type A insulin resistance-acanthosis
- B. Acquired defects of insulin action
  1. Endocrine tumors-rare in childhood
     a. Pheochromocytoma
     b. Cushing
     c. Others
  2. Anti-insulin receptor antibodies

VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency.
- A. Prader-Willi syndrome, chromosome 15
- B. Down syndrome, chromosome 21
- C. Turner syndrome
- D. Klinefelter syndrome
- E. Others
  1. Bardet-Biedel
  2. Alstrom
  3. Werner

IX. Gestational diabetes

X. Neonatal diabetes
- A. Transient-cyclic adenosine monophosphate maturation, chromosome
- B. Permanent-agenesis of pancreas
  - glucokinase deficiency, homozygous

Table 1: Etiologic Classification of Diabetes Mellitus Epidemiology

Internationally, there is variation in the incidence and prevalence of T1DM by race, age, season and geographic location. The explanation for these variations is still unclear. Many countries report that incidence rates have doubled in the last 20 years.[6] The rates are highest in Scandinavia especially Sardinia and Finland with annual incidence of 34.4 cases/ 100,000 and 40 cases/ 100,000 respectively.[7] In the US, incidence is 15 cases per 100,000 annually and 13.5/100,000 in the United Kingdom.[8] Incidence figures are lowest in Asia and Africa. In China, annual incidence is 1/100,000 and 7.8/100,000 in Libya.[8] In Nigeria, there is a relatively high prevalence rate of 0.33/1000 among school children despite potential deaths caused by minimal medical attention.[9] This is probably due to long-term protein malnutrition and endemic childhood infections, which have been implicated in the aetiology of IDDM in similar populations.

The onset of T1DM has a bimodal pattern with peak incidence at the age of 6-8 years and during puberty but onset in the first year of life is unusual.[10] There is no sex predominance.

The onset of T1DM is seasonal with peak in fall and winter months. This has been suggested as evidence for viral aetiology, but it may also be due to seasonal pattern of higher blood glucose in normal persons during winter.[11]

Pathogenesis

The precise aetiology of T1DM is unknown but some contributory factors have been identified.

Role of autoimmune process

T1DM occurs as a result of environmental factors interacting with a genetically susceptible person. The interaction leads to autoimmune disease directed at the insulin-producing β cells of the pancreatic islets of Langerhans and β cell destruction occurs.[12] B-cell and T-cell autoimmune markers are usually present before the onset of disease suggesting that the autoimmune damage is often insiduous.[13] B-cell marker, Islet cell antibody (ICA) is found in 90% of newly diagnosed patients and can be present 20 yrs earlier in at risk groups.[14] Insulin antibodies (IA) occur at disease onset in younger patients while glutamic acid decarboxylase (GAD) antibodies occur in 60-90% of new cases.[14] Insulin deficiency occurs with 90% destruction of β cells which eventually leads to absolute insulinopenia.

Genetic Role

T1DM is not inherited. It is a multifactorial disease with a strong genetic component that is thought to interact with specific environmental triggers. The role of genetic factors in the aetiology is supported by the 30 to 50% concordance rate in monozygotic twins.[15] Several genetic determinants of T1DM have been established. The HLA class II DQ locus on chromosome 6 is the most important, encoding highly polymorphic antigen-presenting proteins that account for almost 50% of the genetic risk for T1D.[14-15] More recently, high-density genome-wide association studies have been performed to search for the remaining T1DM loci.[16] In all, 18 loci have been identified to date as being robustly associated with the pathogenesis of the disease.[16-17]

Role of environmental factors

There is 50% to 70% discordance rate of T1DM in identical twins, suggesting that environmental factors may trigger the disease in genetically susceptible individuals.[18] Implicated trigger factors are viruses such as enteroviruses, rubella, coxsackie B, cytomegalovirus, mumps which are postulated to directly initiate damage to β cells.[19] Exposure to certain chemical toxins and drugs that specifically destroy pancreatic cells, such as, rodenticide vacor and streptozotocin, lead to disruption of insulin production.[20] Furthermore, breastfeeding seems to provide protection against the risk of developing T1DM, possibly by direct effect and delayed introduction of cow's milk. It has been proposed that bovine serum albumin, a protein in cow's milk with properties similar to islet cell antigen, stimulates autoantibody production leading to destruction of islet cells.[21]

Pathophysiology

Progressive destruction of β cells leads to progressive insulin deficiency. In normal metabolic state, there are regular swings between the postprandial high insulin anabolic state and fasted low-insulin catabolic state that affect three major tissues: liver, muscle and fat as shown in table 2 below.[2]

	High Insulin (Postprandial state)	Low Insulin (Fasting state)
Liver	Glucose uptake Glycogen synthesis No gluconeogenesis Lipogenesis No ketogenesis	Glucose production Glycogenolysis Gluconeogenesis Ketogenesis No Lipogenesis
Muscle	Glucose uptake Glycogen synthesis Protein synthesis	No Glucose uptake Glycogenolysis Proteolysis & Amino acid release
Adipose Tissue	Glucose uptake Lipid synthesis Triglyceride uptake	1No Glucose uptake Lipolysis & Fatty acid release No triglyceride uptake

Table 2: Glucose homeostasis – Comparison of Fed and Fasting States

T1DM as it evolves becomes a permanent low-insulin catabolic state in which feeding exaggerates the catabolic state.[2] The failure to secrete insulin results in an inability to oxidize glucose in muscle and adipose tissue. There is increase in counter regulatory hormones such as cortisol, adrenaline, glucagon and growth hormone which lead to further rise in blood glucose and accelerate the rate of metabolic decompensation.[22] The resulting hyperglycaemia leads to osmotic diuresis, glycosuria and thirst when the renal threshold for glucose is exceeded. The osmotic diuresis results in polyuria and secondary polydipsia. Untreated patients excrete high glucose load causing polyphagia[2] Dehydration occurs when fluid losses exceed intake. Furthermore, insulin deficiency leads to lipolysis with production of excess free fatty acids and ketone bodies leading to ketonuria and metabolic acidosis resulting in compensatory deep rapid breathing (kussmaul respiration).[23] Coma may occur due to ketosis, acidosis, dehydration and hyperosmolality.[23]

Clinical Presentation
The classical presenting symptoms of T1DM are polyuria, polyphagia, polydipsia, weight loss and lethargy.[24] Onset may be acute, precipitated by an acute illness, or more chronic and insidious over weeks or even months.[24] Hyperglycemia impairs immunity and renders a child more susceptible to recurrent infections, particularly of the urinary tract, skin, and respiratory tract. Candidiasis may occur, especially in groin and flexural areas.[2] Other features are constipation, anorexia

and blurred vision but the younger children, less than 5 years of age are usually asymptomatic except for nocturnal enuresis.[22] There is therefore need for high index of suspicion in this age group to prevent late diagnosis and its consequences such as diabetic ketoacidosis (DKA). In the developing countries, most children present for the first time in DKA partly because of lack of recognition of their symptoms by health workers.

Diagnosis of Diabetes Mellitus
There was a recent revision of the criteria for the diagnosis of DM by the American Diabetes Association's (ADA) with the definition of a new threshold for the diagnosis of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). The criteria for diagnosis of DM include the presence of at least of one of the following:[25]

(i) Symptoms of hyperglycaemia including polyuria, polydipsia, weight loss plus random plasma glucose concentration >200 mg/dl (11mmol/L).

(ii) Fasting (> 8 hours) plasma glucose > 126 mg/dl (7 mmolL).

(iii) 2 hour postprandial glucose >200 mg/dl during an oral glucose tolerance test (OGTT).

Criteria for diagnosing IGT and IFG are 2 hour plasma glucose between 140-200 mg/dl (8-11 mmol/L) or a fasting glucose between 100-125 mg/dl (6-7mmol/L) respectively.[25-26]

Early Clinical Course
The natural history of T1DM is in 4 phases of β cell functional capability.[27, 29]
• Insulin deficiency at clinical presentation.
• Remission – partial/complete: Within a few weeks of starting insulin therapy, approximately two thirds of children enter a remission ('honeymoon') period during which endogenous insulin production increases. Remission can last weeks to months.[27]
• Relapse - There is irreversible loss of insulin secretory capacity in patients with remission with abrupt increase in insulin requirement. This can occur gradually or abruptly as a result of intercurrent infections.[27,29]
• Total diabetes occurs when there is complete insulin deficiency as a result of lack of endogenous insulin secretion. Glycaemic control with subcutaneous insulin becomes more difficult and glycemic excursions more profound.[27]

Investigations
At initial diagnosis of T1DM, it is important to carry out investigations such as:
1. Blood glucose: Diagnosis is confirmed when there are classic symptoms and one random blood glucose

greater than 200 mg/dl, confirmed on a subsequent day, or fasting blood glucose greater than 126 mg/dl on two occasions.[28]

A formal oral glucose tolerance test is rarely necessary for diagnosis of T1DM. It can exclude the diagnosis of diabetes when hyperglycemia or glycosuria occur as a result of intercurrent illness, steroid therapy or when the patient's condition includes renal glucosuria.[2, 28] Stress hyperglycemia (a transient increase in blood glucose during acute stress) may be differentiated from new onset diabetes by its short duration (1-5 hours) and without insulin treatment, glucose levels return to normal.

2. Urine glucose: Glycosuria is suggestive of DM and not diagnostic.[22]

3. Urine ketones: Ketonuria is a marker of insulin deficiency and potential DKA. Its presence generally confirms that diabetes is T1DM.[22]

4. Islet cell antibodies, IA and GAD may be present at diagnosis but are not needed to diagnose T1DM.[2]

Management of Type 1 Diabetes Mellitus

Managing children and adolescents with DM is complex and requires multidisciplinary team including a paediatrician with expertise in diabetes, diabetes nurse specialist, dietitian, psychologist, health educator and social worker.[24, 30] The goals of treating a child with DM are to achieve (i) normal growth and development, (ii) prevent acute complications such as severe hypoglycaemia which when recurrent, is associated with risk of developing learning disabilities and neurologic deficits in children less than 5years and (iii) prevent chronic complications by achieving near normal blood glucose.[24] Duration of hyperglycaemia is the most important risk factor for chronic complications of T1DM. The management of DM can be divided into long term management and management of acute complications primarily diabetic ketoacidosis (DKA).

Long Term Management

At initial diagnosis, hospitalization may not always be required except in children with the following conditions: (i) diabetic ketoacidosis, (ii) age less than 5 years, (iii) parents with difficulty understanding the management program and/or serious psychosocial problems, (iv) children with psychomotor delay, (v) families who live outside the region.[30]

The basic components of long term management of T1DM are education and emotional support, diet and insulin therapy.

Education

Education is a continuous process at every stage of the life of the child and the family. It should involve all members of the diabetes team. Education should be formal sessions in a clinic or hospital ward setting and opportunistic teaching at clinics or at home in response to crises or difficulties such as acute illness.[29] A teaching program should be set up for the child and the family to understand the basic pathophysiology of diabetes and the importance of adequate metabolic control to avoid acute and chronic complications. They should be provided with the skills necessary for managing children safely at home, basic skills for survival including insulin administration, blood glucose monitoring, recognition and treatment of hypoglycemia, hyperglycemia, and ketoacidosis, adjusting insulin and diet for growth, exercise, and sick days.[28-29] They should be encouraged to establish appropriate behaviours for maintenance of glycaemic control in early childhood which facilitates compliance during puberty. They should not be overwhelmed with information initially and printed educational material should be used to facilitate long term mastery.[28-29]

Dietary Management

This is an essential component of diabetes care. A paediatric dietician should provide education, monitoring, and support to the child, parents and extended family.[31] The dietician should advise on planning, content, and timing of snacks/meals in the context of each child's individual circumstances, lifestyle, and the insulin action profiles. The dietary recommendations should be based on healthy eating recommendations appropriate for all children and adults and the whole family should be encouraged to make appropriate changes.[29,31-32] Basic universal recommendations are that carbohydrates should provide 50-60% of daily energy intake and no more than 10% should be from sucrose or other refined carbohydrates. Fat should provide less than 30% and protein should provide 10-20% of daily intake.[29,33] The aim is to balance the child's food intake with insulin dose and activity and to keep blood glucose concentrations as close as possible to reference ranges of 80-180mg/dl.[31] The diet plan should be developed for each child to suit individual needs and circumstances and reviewed regularly.

Insulin Therapy

Insulin is required for treating all forms of diabetes. It was isolated in 1921-22 at the University of Toronto by Banting, Macleod, Best and Collip. There are 3 species of insulin - Porcine, Bovine and Human insulin. Their onset of action, efficacy and side effects are similar, but human insulin is recommended for children with diabetes.

Advances in Insulin Therapy

The most recent advance in insulin therapy was the development of insulin analogues with the overall aim that administered insulin would mimic the physiological release of insulin during the post-prandial and post-absorptive periods.[34-35]

preferred by children as they are quicker and easier to use than syringes and needles.[28] Insulin can also be administered with insulin pumps. They are programmable pumps containing insulin connected by infusion line to a small plastic cannula inserted subcutaneously.[28]

Duration	Time to Onset	Time to Peak	Duration of action (hrs)	Examples
Ultra-long-acting (LA)	1-2 hrs	10-14 hrs	23-24	Glargine, Detemir
Intermediate-acting (IA)	30-60mins	4-8 hrs	8-12	Insulatard
Short-acting (SA)	30mins	1-2 hrs	6-8	Human Actrapid
Ultra-short-acting (RA)	10 mins	30-60mins	2-5	Novorapid Lispro

Table 3: Onset and Duration of Action of Insulin Analogues

Table 3 shows currently available insulin analogues, their onset and duration of action.

Ultra-short acting insulin analogues are very rapid-acting (RA) and exist as monomers, thus absorbed in minutes. They are injected immediately before food and allow for greater flexibility of meal time. This leads to improvement in glycaemic control with fewer episodes of hypoglycaemia.[34-35] Examples of ultra-long-acting insulin analogues are Ultralente, Glargine. They lead to consistent and prolonged insulin release with no peaks and constant basal insulin concentration. This leads to better glycaemic control, less nocturnal hypoglycaemia and good safety data.[35-36]

Many non-invasive routes for insulin administration have been investigated including nasal, buccal, oral, gastrointestinal, and transdermal. There has been maximum progress with the inhaled route.[37] It is an insulin analogues with the aim of delivering insulin in more convenient manner than the traditional subcutaneous route, thus it may be especially useful for patients with needle phobia.[38] It has been shown that when inhaled insulin is taken before meals in addition to a basal insulin injection, it leads to good glycaemic control similar to that of patients given multiple dose injections (MDI).[39] However, the long term safety and efficacy of inhaled insulin is yet to be established.[24]

Insulin Delivery Devices

Insulin can be delivered with syringe and needle. Semiautomatic pen injector devices, disposable (prefilled) or reusable are now available and generally

Insulin Regimens

The aim of insulin therapy is to mimic the physiological secretion of insulin. At diagnosis, as a rule of thumb most pre-pubertal children will require 0.5 to 1 unit/kg/day of insulin. Adolescents may require up to 2 units/kg/day.[28] This requirement may be reduced substantially in the first few months of therapy during the honeymoon period.[28] There are various regimens. When choosing a regimen, we should bear in mind the needs and wishes of the family and make changes, if there are difficulties or poor glycaemic control.

1. Traditional regimen – this is the use of twice daily injection using a mixture of ultra-short-acting (RA) or short-acting (SA) and intermediate-acting (IA) insulin. About one third is given as RA/SA and two-third as IA formulation. About 60-70% of total daily dose is given before breakfast and 30-40% is given before supper.[2]

2. The Basal/bolus regimen – Basal bolus regimen can be given by multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) which uses only rapidly acting insulin. MDI is the use of RA/SA prior to each main meal with an injection of LA prior to bedtime. It suppresses glucose production between meals and overnight. Usually 30% to 40% of total daily dose of insulin is given at bedtime as LA and 60% to 70% is given as RA/SA and split between the three meals. It allows greater variation in meal times and size of meals.[36,40]

3. Continuous Subcutaneous Insulin Infusion (CSII) – the use of insulin pump therapy. It is used in about 25% of children in the USA and about 1-2 % in the United Kingdom. They may be used as

part of an intensive management regimen to improve glycaemic control. The devices consist of a programmable pump containing insulin connected by an infusion line to a small subcutaneous cannula. One injection site is used for 2-4 days, hence there is less variation in absorption due to site rotation and insulin delivery allows closest match to physiological requirements. The pump delivers RA/SA insulin continuously at a basal rate with additional boluses delivered at meal time. Pump therapy is said to provide the best and most consistent glycaemic control. It should be used only by a trained and experienced team.[28,40]

Problems of Insulin therapy
- Somogyi phenomenon – This is the rebound morning hyperglycaemia which may occur following nocturnal hypoglycaemia caused by release of counter regulatory hormones (GH, glucagon, cortisol & adrenaline).[22]
- Dawn phenomenon - This is hyperglycaemia as a result of hypoinsulinaemia which occurs between 5-9am. It occurs mainly in puberty and is thought to be due to insulin resistance caused by nocturnal GH secretion.[22]

Blood glucose monitoring
The level of long term glycaemic control determines significantly the risk of developing chronic microvascular complications of diabetes, therefore, it is important to maintain blood sugars as near normal as possible and prevent the risk of hypoglycaemia. Therefore, regular home blood glucose monitoring should be carried out for the success of intensive management of diabetes.[24] Generally, a blood glucose level of 100-200mg/dl (6-12 mmol/L) for preschool children, 72-180mg/dl (4 -10 mmol/L) for older children and 72-144mg/dl (4 -8 mmol/L) for adolescents should be the aim.[24]

Routine follow up
Children and their parents should be seen regularly in a designated clinic for follow up by the diabetes team every 3 to 4 months and assessed for the following:[28,30]
- general health, including height, weight, blood pressure, hospital admissions;
- Review of blood glucose monitoring, insulin regimen and details of hypoglycaemic episodes
- comparison of glycemic control with glycosylated hemoglobin (HbA$_{IC}$)
- accuracy of the glucose monitor compared with laboratory blood glucose testing equipment;
- meal plan requirements and adherence;
- knowledge of diabetes, insulin, and diet;
- insulin injections and examination of injection sites
- attitudes to and management of diabetes, psychosocial problems and school progress

Children should also be screened for conditions associated with diabetes and for long-term complications.

Patients who have had diabetes for 2 years or more should have annual review with physical examination for microvascular & other complications of DM including fundoscopy as detailed in table 4.

System	Points to note
Height	Growth failure
Weight	Poor or excessive weight gain
Puberty	Delayed puberty/menarche
Skin	Lipohypertrophy; necrobiosis lipoidica
Mouth	Dental caries or signs of poor oral hygiene
Eyes	Retinopathy/cataracts
Feet	Signs of poor foot care e.g. calluses
Hands	Limited joint movement
Cardiovascular	Hypertension
Endocrine	Goitre, signs of hypo- or hyperthyroidism
	Hyperpigmentation of Addison's disease
Neurological	Impaired vibration and pinprick sense; loss of ankle reflex

Source – Reference 28

Table 4: Points to note on examination of patients with DM at annual review

They should also have the following investigations:[28,30]
1. Glycated hemoglobin (HBA1c) - best method for medium- to long-term diabetic control monitoring. Levels should be checked every 3 months. Most clinicians aim for HbA1c values of 7-9%.
2. Thyroid function tests - Untreated thyroid disease may interfere with diabetes management so thyroid function should be checked annually if thyroid antibodies are present.
3. Screening for coeliac disease by measurement of celiac antibodies annually.
4. Screening for microalbuminuria - From age 12 years, annual urinalysis needed to test for a increased albumin excretion rate (AER), referred to as microalbuminuria, which is an indicator of risk for diabetic nephropathy
5. Lipid profiles - Children should also be screened intermittently for lipid abnormalities (fasting serum lipid profile 6 months after diagnosis and again during adolescence or when diabetic control is poor.
6. Renal function tests: If the child is otherwise healthy, tests typically are not required.

Complications of Type1 Diabetes Mellitus

There are 3 major categories:

- Acute complications - reflect the difficulties of maintaining a balance between insulin therapy, dietary intake, and exercise.
- Long-term complications - Chronic complications of diabetes in childhood and adolescent result from poor glycaemic control. Complications include short stature with delayed maturation, limited joint mobility commonly affecting the interphalangeal joints and adolescent microvasculopathy, neuropathy and microalbuminuria.
- complications caused by associated autoimmune diseases

Acute Complications

These include: DKA, hypoglycemia, and hyperglycemia. The commonest acute complication of T1DM is DKA and will be discussed in detail.

Diabetic Ketoacidosis (DKA)

Diabetic Ketoacidosis creates a life-threatening medical emergency. Therefore, early recognition and careful management are essential if death and disability are to be avoided. DKA may be the initial presentation of T1DM and is the most important cause of mortality and severe morbidity in children with diabetes, particularly at the time of first diagnosis.[22] In Africa, it is the most frequent cause of death in patients with T1DM. It may occur as a result of an intercurrent illness or recur if insulin is omitted (recurrent DKA in adolescence is almost always due to insulin omission).[23] The clinical features of DKA are severe dehydration, shock, frequent vomiting, polyuria despite dehydration, weight loss in spite of good intake, acetone breath – (Kussmaul respiration) deep and rapid, altered sensorium and signs of raised intracranial pressure such as bradycardia, hypertension and anisocoria.[22-23] Diagnosis can be made on clinical and biochemical grounds. The biochemical criteria for the diagnosis of DKA include hyperglycemia (glucose >200mg/dl/ 11mmol/l), metabolic acidosis (bicarbonate < 15mmol/) and venous PH <7.30 with ketonuria (serum ketones >5mmol/l).[28]

Management of DKA

DKA is a medical emergency and like all emergencies, resuscitation should follow the 'ABC' pattern. The protocol described is largely based on that published by the European Society for Paediatric Endocrinology and the Lawson Wilkins Paediatric Endocrine Society[41] and by the British Society for Paediatric Endocrinology and Diabetes.[42]

Resuscitation
- Admit to the intensive care unit or high dependency unit if pH<7.00, age < 2 years, unconscious and blood glucose >1000mg/dL
- Resuscitation in ABC pattern
- If in shock, oxygen by face mask should be given.
- If signs of shock (i.e hypotension, severe peripheral shut-down, oliguria) are present, resuscitate with boluses of 10 ml/kg of 0.9% saline, or 0.9% saline plus 5% albumin. Repeat as necessary, and then place on maintenance + deficit.
  Replace fluid requirement over 48 hours. If the corrected serum sodium value is in the hypernatraemic range, even slower rehydration may be considered.

Initial Monitoring

- Hourly pulse rate, respiratory rate, blood pressure, neurological observations.
- Hourly blood glucose measurement while on an insulin infusion.
- Accurate fluid balance (an indwelling catheter may be required).
- 2-4 hourly temperature
- Test all urine for ketones until negative.
- Strict fluid balance is essential. Reassess fluid status every few hours. Continuing polyuria may worsen the dehydration if a positive fluid balance is not being achieved. The patient initially should be "Nil by Mouth.
- Insert a sampling cannula and obtain blood samples for:
- Baseline blood glucose, electrolytes, calcium, phosphorus, venous pH and acid base status (arterial if signs of shock are present), full blood count, urea and creatinine, triglycerides and sepsis work up if indicated.
- urine test for ketones and microscopy, culture and sensitivity.
- Do 2-4 hourly electrolytes and venous pH, depending on severity and progress.

Electrolyte Replacement
- Sodium replacement is individualised on the basis of biochemical monitoring. The measured serum sodium concentration is lowered by the dilutional effect of the coexistent hyperglycaemia and coexistent hyperlipidaemia. An approximate corrected sodium can be calculated as follows:
  Corrected sodium = $\frac{\text{Sodium} + 1.6(\text{glucose} - 5.5)}{5.5}$
  (all values in mmol/l)

- If corrected sodium is greater than150 mmol/L, correction of the dehydration and electrolyte imbalance over 48-72 hours is advocated to minimize the risk of cerebral oedema.
- Potassium replacement should be started as soon as resuscitation is completed and prior to commencing the insulin infusion. If renal failure is suspected, withhold potassium until electrolytes are available and an indwelling catheter is inserted.
- Commence potassium chloride at 5 mmol/kg/day Check serum potassium 2 hours later and then 4 hourly.
- Bicarbonate therapy is generally not required. It may be considered after consultation in the severely shocked patient with severe acidosis (i.e. arterial pH <7.0 and/or HCO_3 <5mmol/L). Cardiac monitoring is required; hypokalaemia and exacerbation of hypernatraemia are risks. Bicarbonate should be given by an intravenous infusion over 30 minutes.

Insulin Infusion
- Start after resuscitation is completed and rehydration and potassium replacement is under way.
- Add 50 units of short-acting insulin to 500 ml of 0.9% Saline, so that 10 ml of solution will contain 1 unit of insulin. If an infusion pump is not available, a soluset may be used.
- The insulin infusion must be clearly labeled so that confusion with the rehydrating solution does not occur.
- Start the insulin infusion at 0.05-0.1 units/kg/hr. It is not necessary to give a priming bolus of insulin.
- The aim is to produce a fall in blood glucose of 72-90mg/dl (4-5 mmol/L) per hour. Over the first two hours, however, rehydration alone will result in a fall in blood glucose and a larger fall can be accepted at this time without a reduction in insulin infusion rate.
- If plasma glucose concentrations fall by more than 90mg/dL/hour add dextrose (5-10%) to the intravenous fluids.
- When the blood glucose has fallen to 14-17 mmol/L (250-300mg/dL), intravenous fluid with dextrose should be prescribed (usually a 5% dextrose/0.45% saline mixture is used, but dextrose concentrations of up to 10% may be necessary to maintain plasma glucose concentrations).
- The insulin infusion rate and/or the Dextrose infusion rate should then be adjusted to keep the blood glucose level between 140 – 220 mg/dl (8-12 mmol/L).

- The insulin infusion should not be stopped before the acidosis is corrected as insulin is required to switch off ketone production. If the blood glucose falls <4mmol/L., (<72mg/dL) a bolus of 2ml/kg of 10% dextrose should be given and the dextrose concentration in the fluid increased.
- When the pH is >7.30, the blood glucose concentration has been reduced to 14-17 mmol/L (250-300mg/dL), and a dextrose infusion has been started, the insulin infusion rate can be reduced – but not to less than 0.05 units/kg/hour.
- If the patient still requires IV fluids after 24 hours, use 0.45% saline in 5% Dextrose.

Subsequent Management
- Although plasma glucose concentrations may fall to near normal levels within 4-6 hours of treatment of DKA, the metabolic acidosis may take 24 hours or longer to resolve.
- Blood gases and electrolyte and urea concentrations should be re-evaluated 2 hours after the start of treatment and 4-hours thereafter, or more frequently if there are clinical concerns, until the child has recovered.
- The ongoing intravenous fluid prescription should be reviewed every 4 hours and adjusted according to the electrolyte results and fluid balance.
- If there is continuing massive polyuria, the rate of infusion of intravenous fluids may need to be increased and large gastric aspirates will need replacing with 0.45% saline with 10mmol/L potassium chloride
- Once the blood gases and electrolyte concentrations normalize, the frequency of blood sampling can be decreased and discontinued once the child is tolerating oral fluids and food.
- The frequency of bedside capillary blood glucose measurements may be reduced to 2-to-4-hourly if plasma glucose concentrations are relatively stable while the child is receiving intravenous dextrose.
- If the acidosis or hyperglycaemia do not improve after 4-6 hours the patient should be reassessed by a senior doctor. Insulin errors, inadequate rehydration or sepsis may be the cause. More insulin, 0.9% saline or antibiotics may be required.
- Intravenous fluids should be continued until the child is drinking well and able to tolerate snacks.
- The insulin infusion should be continued until significant ketonuria (+++) is no longer present. However, it is not necessary to wait for complete resolution of ketonuria before changing to subcutaneous insulin.
- When the patient is started on a conventional subcutaneous insulin regimen, the insulin infusion should be discontinued 30 minutes (if using a short

and long-acting insulin) after the first subcutaneous injection to avoid rebound hyperglycaemia.

Cerebral Oedema
This can be a sudden and unpredictable complication of the therapy of DKA which occurs in the first 24 hours of treatment. It is commoner in children younger than 10 years (especially < 5 years).[2] The aetiology is poorly understood because it could occur even with optimum management of DKA.[28] It is associated with 25% mortality and neurological sequelae in survivors.[28] All patients should therefore be monitored for signs and symptoms of raised intracranial pressure. Risk factors and warning signs include severe dehydration and shock, severe acidosis and low serum potassium indicating severe total body loss of potassium, hypernatraemia indicating a hyperosmolar state, hyponatraemia, and deteriorating conscious state during therapy.[43,44]
If suspected it requires treatment immediately with mannitol 1-2 g/kg by intravenous infusion over 20 minutes. The rate of fluid administration should be reduced. Transfer to an intensive care facility and arrange a neurological assessment and CT scan.[43,44]

Prospects for the Cure of Type 1 Diabetes
The mainstay of treatment for T1DM is currently lifelong insulin therapy. However, cure of the disease is being sought through various treatment protocols including those aimed at replacing ß cells via pancreatic organ transplantation or islet cell transplantation. These are:
- Efforts at prevention and early diagnosis through genetic and immunologic screening of high-risk children.
- Development of new and improved insulins.
- Administration of insulin by alternate routes like nasal, inhalation.
- Improvement in the management and outcome of pancreatic and islet cell transplantation.[28]

Pancreatic and islet cell transplantation
Pancreatic transplantation was first reported in 1966 with significant improvement in operative techniques and immnosuppressive drugs over the years.[45] Pancreatic transplantation is not generally recommended in children because of the risks of surgery and prolonged immunosuppression.[46] Successful islet cell transplantation was first reported in 1980 and recent advances in immunosuppressive therapy and transplant biology with the development of the regimen called Edmonton protocol led to very good result of 80% rate of insulin independence and euglycaemia at 1 year post-transplant. However, longer term follow up has tempered enthusiasm for this strategy.[47]

Techniques are now underway to develop stem cell therapy to isolate and propagate islet cell progenitor cells from adult pancreas or extrapancreatic sources suitable for transplantation.[48]

In conclusion, T1DM is not uncommon in African children despite the paucity of data on the epidemiology in Africa. It is an autoimmune disorder that is usually triggered by some environmental factors in genetically susceptible individuals. DKA may be the initial presentation of T1DM and is the most important cause of mortality and severe morbidity in children with diabetes, particularly at the time of first diagnosis. In Africa, it is the most frequent cause of death in patients with T1DM. The risk of complications relates to diabetic control. With good management, patients can expect to lead full, normal, and healthy lives. Mortality and morbidity associated with T1DM diabetes has perceptually declined with the identification and widespread use of newer insulins and automated methods of delivery via programmable pumps. Furthermore, there are prospects in islet cell transplantation and the development of stem cell therapy for future cure of the disease.

Sadly, this remarkable achievement has not reached the children who develop diabetes in sub-Saharan Africa where the onset of childhood diabetes may be the equivalent of a death sentence. Two major issues of importance related to T1DM in developing countries are missed diagnosis and unavailability of insulin.

REFERENCES
1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2000; 23: S4.

2. **Sperling MA.** Diabetes Mellitus. In: Sperling MA, editor. Pediatric endocrinology. 2nd ed. Philadelphia: Saunders; 2002. p. 323-366.

3. **Devendra D,** Liu E, and Eisenbarth GS. Type 1 diabetes: recent developments. BMJ 2004; 328 : 750-754

4. **Freugel P,** and Velho G. Molecular genetics of maturity-onset diabetes of the young. Trends Endocrinol Metab 1999; 10:142.

5. **Aguilar-Bryan L** and Bryan J. Neonatal Diabetes Mellitus. Endocrine Reviews 2008; 29:265–291.

6. **Hamman RF,** Cay EC, and Cruickshank KJ: Colorado IDDM registry. Incidence and variation of IDDM in children ages 0 – 17 years. Diabetes Care 1990; 13:499.

7. **Silink M.** Childhood Diabetes: a global perspective, Hormone Res 2002; 57: 1-5

8. **Karvonen M,** Tuomilehto J, Libman J, and LaPorte R. A Review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus. World Health Organization DIAMOND Project Group, Diabetologia 1993; 36:883.

9. **Afoke AO,** Ejeh NM, Nwonu EN, Okafor CO, and Udeh NJ, Ludvigsson J. Prevalence and clinical picture of IDDM in Nigerian Igbo schoolchildren. Diabetes Care. 1992; 15: 1310-1312.

10. **Karjalainen J,** Salmela P, Ilornen J, *et al.* Comparison of childhood and adult type I diabetes mellitus. N Engl J Med 1989; 320: 881.

11. **MacDonald NJ.,** Liston L, and Carlson I. Seasonality in glycosylated hemoglobin in normal subjects. Diabetes 1987; 36: 65

12. **Eisenbarth GS.** Type I diabetes. Clinical implications of autoimmunity. Hosp Pract 1987; 167.

13. **Eisenbarth GS.** Type I diabetes. A chronic autoimmune disease. N Engl J Med 1986; 314:1360.

14. **Elfving M,** Lindberg B, Lynch K, Månsson M, Sundkvist G, Lernmark A, and Ivarsson SA. Number of islet autoantibodies present in newly diagnosed type 1 diabetes children born to non-diabetic mothers is affected by islet autoantibodies present at birth. Pediatr Diabetes. 2008; 9:127-134.

15. **Kelly MA,** Mijovic CH, and Barnett AH. Genetics of type 1 diabetes. Best Pract Res Clin Endocrinol Metab 2001; *15* : 279-291.

16. **Grant SF,** and Hakonarson H. Genome-wide association studies in type 1 diabetes. Curr Diab Rep. 2009 Apr;9(2):157-163.

17. **Ounissi-Benkalha H,** Polychronakos C. The molecular genetics of type 1 diabetes: new genes and emerging mechanisms. Trends Mol Med. 2008 Jun;14(6):268-275

18. **Haller MJ,** Atkinson MA, and Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. Pediatr Clin North Am 2005; 52:1553-1578.

19. **van der Werf N,** Kroese FG, Rozing J, and Hillebrands JL. Viral infections as potential triggers of type 1 diabetes. Diabetes Metab Res Rev. 2007;23:169-183

20. **Esposti MD,** and Ngo A, and Myers MA. Inhibition of mitochondrial complex I may account for IDDM induced by intoxication with the rodenticide Vacor. Diabetes. 1996; 45:1531-1534.

21. **Luopajärvi K,** Savilahti E, Virtanen SM, Ilonen J, Knip M, Akerblom HK, Vaarala O. Enhanced levels of cow's milk antibodies in infancy in children who develop type 1 diabetes later in childhood. Pediatr Diabetes. 2008; 9: 434-441.

22. **Glasgow AM.** Diabetes Mellitus. In Wellington Hung, editor. Clinic Pediatric Endocrinology. St Louis: Mosby; 1992; 317-318.

23. **Sperling MA.** Diabetic ketoacidosis. Pediatr Clin North Am 1984; 31: 591.

24. **Dejkhamron P,** Menon RK, and Sperling MA. Childhood diabetes mellitus: Recent advances & future prospects. Indian J Med Res 2007; 125: 231-250.

25. Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006; 29: S43-48.

26. **Genuth S,** Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, *et al.* Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160-3167.

27. **Sherry NA,** Tsai EB, and Herold KC. Natural History of {beta}-Cell Function in Type 1 Diabetes. Diabetes 2005; 54: S32 - S39.

28. **Raine JE,** Donaldson MC, Gregory JW, Savage MO, and Hintz RL. Diabetes Mellitus. Practical Endocrinology and Diabetes in Children. 2nd ed. Oxford: Blackwell; 2006. 1-32.

29. Clinical Guideline 15. Type 1 diabetes: diagnosis and management of type 1 diabetes in children,

young people and adults. NICE Guideline. July 2004.

30. **Curtis JA,** and Hagerty D. Managing diabetes in childhood and adolescence. Can Fam Physician 2002; 48: 499-509.

31. **Aslander-van Vliet E,** Smart C, and Waldron S. Nutritional management in childhood and adolescent diabetes. Pediatric Diabetes 2007: 8: 323–339.

32. American Diabetes Association. Evidence -based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care 2002: 25: 202–212.

33. American Diabetes Association (statement of the ADA). Nutrition recommendations and interventions for diabetes–2006. Diabetes Care 2006: 29: 2140–2157.

34. **Rachmiel M,** Perlman K, and Daneman D. Insulin analogues in children and teens with type 1 diabetes: advantages and caveats. Pediatr Clin North Am 2005; 52: 1651-1675.

35. **Hirsch IB.** Insulin analogues. N Engl J Med 2005; 352:174-183.

36. **Williams RM,** and Dunger DB. Insulin treatment in children and adolescents. Acta Paediatr 2004; 93: 440-446.

37. **Owens DR,** Zinman B, and Bolli G. Alternative routes of insulin delivery. Diabet Med 2003; 20: 886-898.

38. **Rungby J,** Brock B, and Schmitz O. New strategies in insulin treatment: analogues and noninvasive routes of administration. Fundam Clin Pharmacol 2005; 19: 127-132

39. **Odegard PS,** and Capoccia KL. Inhaled insulin: Exubera. Ann Pharmacother 2005; 39: 843-853.

40. **Renard E.** Intensive insulin therapy today: 'basal-bolus'using multiple daily injections or CSII? Diabetes Metab 2005; 31: 40-44.

41. **Dunger DB,** Sperling MA, Acerini CL, Bohn DJ *et al.* European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society Consensus Statement on Diabetic Ketoacidosis in Children and Adolescents Pediatrics 2004;113:133-140

42. British Society for Paediatric Endocrinology and Diabetes (BSPED). Recommended DKA guidelines 2004. www.bsped.org.uk

43. **Franklin B,** Liu J, and Ginsberg-Fellner F. Cerebral edema and ophthalmoplegia reversed by mannitol in a new case of insulin-dependent diabetes mellitus. Pediatrics. 1982;69:87–90

44. **mn Roberts MD,** and Slover RH, Chase HP. Diabetic ketoacidosis with intracerebral complications. Pediatr Diabetes 2001; 2: 109–114

45. **Bonner-Weir S,** Weir GC. New sources of pancreatic beta-cells. Nat Biotech 2005; 23: 857-861.

46. **Kelly WD,** Lillehei RC, Merkel FK, Idezuki Y, and Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 61: 827-837.

47. **Nanji SA,** and Shapiro AM. Advances in pancreatic islet transplantation in humans. Diabetes Obes Metab 2006; 8: 15-25.

48. **Street CN,** Sipione S, Helms L, Binette T, Rajotte RV, Bleackley RC, *et al.* Stem cell-based approaches to solving the problem of tissue supply for islet transplantation in type 1 diabetes. Int J Biochem Cell Biol 2004; 36: 667-683.